Comparative effective dose of ciprofol and propofol in suppressing cardiovascular responses to tracheal intubation: a single-center, double-blind, randomized, controlled clinical trial

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Article

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Abstract

Ciprofol, a novel γ-aminobutyric acid receptor agonist, outperforms propofol with minimal cardiovascular effects, higher potency, reduced injection pain, and a broader safety margin. Despite these advantages, ciprofol's clinical research is still emerging. This study compares the median effective dose (ED50) and adverse reactions of ciprofol and propofol, in conjunction with sufentanil, for suppressing cardiovascular responses during tracheal intubation. A total of fifty-three adult patients who required general anesthesia for tracheal intubation were enrolled in this study. The patients were randomly assigned to either the ciprofol group (group C) or the propofol group (group P) using a random number table. Tracheal intubation was performed using a standardized laryngoscope and endotracheal tube. The Dixon's up-and-down method was employed to determine the ED50 and 95% effective dose (ED95) of ciprofol and propofol in inhibiting cardiovascular responses during tracheal intubation. Based on the pilot study, the initial dose of ciprofol was set at 0.35 mg/kg (with a dose increment of 0.01 mg/kg) and propofol was set at 2.0 mg/kg (with a dose increment of 0.1 mg/kg). Dose-response curves were generated using probit analysis to establish the ED50 and ED95 required to inhibit cardiovascular responses during tracheal intubation. Adverse events following drug administration were closely monitored. A total of 54 participants were included in the study, with 24 in group C (one participant excluded due to repeated intubation) and 30 in group P. Probit analysis revealed that the ED50 and ED95 of ciprofol for inhibiting cardiovascular responses to tracheal intubation were 0.326 mg/kg (95% CI 0.304-0.337 mg/kg) and 0.349 mg/kg (95% CI 0.337-0.470 mg/kg), and for propofol, 1.541 mg/kg (95% CI 1.481-1.599 mg/kg) and 1.656 mg/kg (95% CI 1.599-1.943 mg/kg). Notably, group C demonstrated more stable hemodynamics during induction and showed a significantly lower incidence of injection pain compared to group P. Ciprofol demonstrated more stable hemodynamics and a lower incidence of adverse events during induction. Ciprofol may potentially be used as a substitute for propofol in a wider range of scenarios. Clinical Trial Registration: hppts://ClinicalTrials.gov; Identifier: NCT06095570 (23/10/2023).

Introduction

Laryngoscope insertion and tracheal intubation, critical steps in anesthesia induction, often cause patient discomfort and significant nociceptive stimulation. These procedures typically induce notable hemodynamic responses, such as tachycardia, hypertension, and increased intracranial pressure. This is attributed to the stimulation of oropharyngeal and peripharyngeal tissues during laryngoscope insertion and tracheal tube placement, leading to sympathetic nervous system activation and increased catecholamine secretion. These processes can cause circulatory fluctuations, particularly risky for patients with cardiovascular and cerebrovascular conditions, potentially leading to severe complications like cerebral hemorrhage or cardiac failure.

Research indicates that the combined administration of sufentanil and propofol assists in mitigating potential adverse cardiovascular reactions during endotracheal intubation. Furthermore, multiple clinical studies have demonstrated the effective attenuation of laryngeal reflexes and reduction in the occurrence
of coughing or laryngospasm after tracheal intubation through the use of propofol as a general anesthetic. Thus, propofol facilitates smoother tracheal intubation during anesthesia induction. Despite the notable advantages of propofol in the field of anesthesia, there exist drawbacks as well, including injection pain, dose-dependent respiratory depression, hypotension, and propofol infusion syndrome. These limitations not only compromise the overall quality of anesthesia but also further constrain the clinical application of propofol.

Ciprofol, a novel phenol derivative ether, enhances GABA-mediated chloride ion influx, offering sedative or anesthetic effects. Early studies highlight ciprofol's advantages over propofol, including minimal respiratory and circulatory impact, higher potency, reduced injection pain, and a broader safety margin. Yet, research on ciprofol's effective dosage for suppressing cardiovascular responses during tracheal intubation is scarce. This study aims to compare the ED50 and safety profiles of ciprofol and propofol in inhibiting cardiovascular reactions during tracheal intubation using an up-and-down method and determine the equipotent dosages of these two drugs, ultimately providing valuable clinical references.

Materials, methods and Ethics

This study has received approval from the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University (LW202282) and has been registered on ClinicalTrials.gov (NCT06095570, 23/10/2023). Prior to participation, all study subjects have obtained informed consent from both the patients themselves and their families, which has been documented through the signing of consent forms.

patient selection

Patients scheduled for elective tracheal intubation under general anesthesia at our hospital, regardless of gender, aged between 18 and 65, with a BMI ranging from 18 to 28 kg/m2, ASA (American Society of Anesthesiologists) class I or II, Mallampati class I or II, normal mouth opening, and normal head and neck mobility will be included. Exclusion criteria comprise the presence of a difficult or potentially difficult airway, uncontrolled or poorly controlled systemic diseases (hypertension, diabetes, e.g.), pregnancy, history of alcohol abuse, allergy to investigational drugs, history of illegal drug use, history of neurological disorders, or inability to effectively communicate. Additionally, failed initial tracheal intubation, emergency situations during induction, and the use of vasoactive drugs are exclusion criteria.

Study design

All patients undergo an 8-hour fasting period before surgery, without specific preoperative medications. In the pre-anesthetic room, patients are granted standard intravenous access and randomly allocated to the Ciprofol (C) or Propofol (P) groups using a random number table. Upon entering the operating room, a reconfirmation of the patient's identity, surgical details, and condition is conducted, while a Dash4000
monitor is employed to monitor vital signs like non-invasive blood pressure (NBP), electrocardiogram (ECG), heart rate (HR), pulse oximetry (SpO₂), and the bispectral index (BIS).

Before anesthesia induction, patients are given oxygen at 6 L/min for 3 minutes. The first patient in group C is intravenously administered Ciprofol Injection (Enterprise: Liaoning Haisi Pharmaceutical Co., Ltd, Batch number: 20220325, IV injection time > 30s) at a dose of 0.35 mg/kg, whereas the first patient in the P group is intravenously administered Propofol Emulsion Injection (Enterprise: Xi’an Libang Pharmaceutical Co., Ltd, Batch number: L06841, IV injection time > 30s) at a dose of 0.2 mg/kg. Once the patient loses consciousness, with the eyelash reflex gone and a Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) score (Table 1) ≤ 1, Sufentanil Citrate Injection (Enterprise: Yichang Renfu Pharmaceutical Co., Ltd, Batch number: 21A11021, IV injection time: 30s) is administered at a dose of 0.25 ug/kg and Rocuronium Bromide Injection (Enterprise: Zhejiang Xianju Pharmaceutical Co., Ltd, Batch number: EA2276, IV injection time: 15s) at a dose of 0.6 mg/kg. Subsequently, under the supervision of a skilled anesthesiologist, a visual laryngoscope is employed for the purpose of intubating the trachea, while a stethoscope is utilized to auscultate and monitor end-tidal carbon dioxide pressure (PetCO2). Mechanical ventilation is initiated post-intubation, adopting a set tidal volume of 6–8 ml/kg and an inspiratory/expiratory ratio of 1:2. The respiratory rate is regulated to maintain an end-tidal carbon dioxide pressure between 35–45 mmHg. 1% sevoflurane is administered for the maintenance of anesthesia following intubation, ensuring that the patient's BIS value remains between 40–60 within 3 minutes, without any form of surgical intervention.

### Table 1. Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale

<table>
<thead>
<tr>
<th>Scale</th>
<th>MOAA/S Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Does not respond to painful trapezius squeeze</td>
</tr>
<tr>
<td>1</td>
<td>Responds only after painful trapezius squeeze</td>
</tr>
<tr>
<td>2</td>
<td>Responds only after mild prodding or shaking</td>
</tr>
<tr>
<td>3</td>
<td>Responds only after name is called loudly and/or repeatedly</td>
</tr>
<tr>
<td>4</td>
<td>Lethargic response to name spoken in normal tone</td>
</tr>
<tr>
<td>5</td>
<td>Responds readily to name spoken in normal tone</td>
</tr>
</tbody>
</table>

Women are intubated using an endotracheal tube with an inner diameter of 7.0, while men are intubated with an endotracheal tube with an inner diameter of 7.5. The anesthesia procedure is conducted by two anesthesiologists and one anesthesia nurse. One anesthesiologist is responsible for intubation and management of potential adverse reactions, while the other anesthesiologist is accountable for recording observation indicators. The anesthesia nurse administers test drugs in accordance with the patient's weight.
The experiment was conducted using an up-and-down method. Based on the preliminary trial, the initial dose for the ciprofol group was determined to be 0.35 mg/kg, with a dose increment of 0.01 mg/kg. For the propofol group, the initial dose was 2.0 mg/kg, with a dose increment of 0.1 mg/kg. The cardiovascular response to intubation dictates the dose adjustment for the next patient. If the cardiovascular response in this case is positive, the next patient will receive an increased dose increment. Conversely, if the response is negative, the dose increment will be reduced. The experiment ends after alternating 8 positive and negative responses in both groups. According to the methods mentioned in relevant literature, the criteria for a positive cardiovascular response is a ≥ 20% fluctuation in SDP/DBP or HR within 3 minutes post-intubation compared to baseline. Otherwise, it is considered a negative response. If the MOAA/S score >1 after intravenous injection of propofol or ciprofol for 3 minutes is also a negative response, prompting continued administration until the score is ≤ 1. During the induction process, if bradycardia occurs (HR < 45 beats/min and lasts > 30s), atropine 0.3 mg will be administered intravenously. If hypotension occurs (a 30% decrease in blood pressure from baseline within 2 minutes), methoxamine 1 mg or ephedrine 3 mg will be administered intravenously.

**Outcomes**

The primary outcome is to determine the ED$_{50}$ and ED$_{95}$ of propofol and ciprofol in suppressing the patient’s response to tracheal intubation during anesthesia induction.

The secondary outcomes include changes in heart rate and blood pressure during tracheal intubation, as well as the occurrence of adverse reactions such as respiratory depression, injection pain, hypotension, allergies, bradycardia, muscle tremors, postoperative nausea, and vomiting during the induction period.

According to the standard for the phase III trial of ciprofol, adverse reactions are defined as follows: (1) hypoxemia (oxygen saturation < 90% for > 30 seconds), (2) bradycardia (heart rate < 45 beats per minute for > 30 seconds), and (3) hypotension (systolic blood pressure decrease by 30% from the baseline value for > 2 minutes).

**Statistical analysis**

IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous variables with a normal distribution were reported as mean ± standard deviation ($\bar{x}$ ± s). Independent sample t-tests or ANOVA were used for between-group comparisons, and paired t-tests for within-group comparisons. Categorical data were expressed as percentages (%) and analyzed using chi-square tests or Fisher’s exact tests. Repeated measures data were evaluated using repeated measures ANOVA. The Probit method calculated the ED$_{50}$, ED$_{95}$, and corresponding confidence intervals (95% CI) of propofol and ciprofol. GraphPad Prism 9 software was utilized to create sequential experiment graphs and fit dose-response curves. A $p$-value less than 0.05 was considered statistically significant.

**Results**
Characteristics of patients

A total of 54 patients were enrolled in this trial, with 24 in group C and 30 in group P. Group C had one exclusion due to repeated tracheal intubation, resulting in a total of 23 patients who completed the study. All patients in group P successfully completed the trial (Fig. 1). No significant differences were found in gender, age, BMI, ASA classification, and Mallampati classifications between groups ($p > 0.05$, Table 2).

### Table 2

General comparison between Group C and Group P ($\bar{x} \pm s$)

<table>
<thead>
<tr>
<th>Group</th>
<th>Group C (N = 23)</th>
<th>Group P (N = 30)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9(39.1)</td>
<td>8(26.7)</td>
<td>0.335</td>
</tr>
<tr>
<td>Female</td>
<td>14(60.9)</td>
<td>22(73.3)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.0 ± 12.3</td>
<td>43.3 ± 10.7</td>
<td>0.596</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.2 ± 2.4</td>
<td>22.5 ± 2.5</td>
<td>0.578</td>
</tr>
<tr>
<td>ASA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>12(52.2)</td>
<td>14(46.7)</td>
<td>0.691</td>
</tr>
<tr>
<td>Class 2</td>
<td>11(47.8)</td>
<td>16(53.3)</td>
<td></td>
</tr>
<tr>
<td>Modified Mallampati score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>13(56.5)</td>
<td>16(53.3)</td>
<td>0.817</td>
</tr>
<tr>
<td>Class 2</td>
<td>10(43.5)</td>
<td>14(46.7)</td>
<td></td>
</tr>
</tbody>
</table>

All data are presented as mean ± standard deviation or n (%). ASA, American Society of Anesthesiologists; BMI, Body Mass Index.

Comparison of dose-response and hemodynamic parameters

Comparison of dose-response

Figure 2 illustrates the positive or negative cardiovascular responses during tracheal intubation in both group C and group P, using the designated dose of the experimental drug for each subject. The x-axis represents the sequence of subject enrollment, while the y-axis represents the dosage of the experimental drug. In group C, 10 patients exhibited positive cardiovascular responses during tracheal intubation, whereas in group P, 13 patients demonstrated positive cardiovascular responses during tracheal intubation.
The ED$_{50}$ and ED$_{95}$ of ciprofol, calculated using the Probit method, for inhibiting cardiovascular responses to tracheal intubation are 0.326 mg/kg (95% CI 0.304 ~ 0.337 mg/kg) and 0.349 mg/kg (95% CI 0.337 ~ 0.470 mg/kg). The ED$_{50}$ and ED$_{95}$ of propofol are 1.541 mg/kg (95% CI 1.481 ~ 1.599 mg/kg) and 1.656 mg/kg (95% CI 1.599 ~ 1.943 mg/kg). The dose-response curves are illustrated in Fig. 3.

**Comparison of hemodynamic variables**

After intravenous administration of the experimental drug to two groups of patients, there was a significant decrease in blood pressure, which returned to baseline levels 1 minute after intubation. In group C, systolic blood pressure (SBP) was significantly lower at T3, T4, T7, and T8 compared to the baseline, while diastolic blood pressure (DBP) was significantly lower at T2, T7, and T8 ($p < 0.05$). In group P, both SBP and DBP were significantly lower before and after intubation compared to the baseline ($p < 0.05$). The heart rate (HR) in group C was significantly lower at T3 compared to the baseline ($p < 0.05$). There were significant differences between group C and group P in terms of DBP and HR ($p = 0.021$ and $p = 0.016$), but no significant difference in SBP (Fig. 4). Post-administration of the drug, HR in group C was lower than in group P ($p = 0.035$); after the administration of all drugs, HR in group C remained significantly lower than in group P ($p = 0.007$), however, both systolic and diastolic pressures in group C were significantly higher than in group P at that time ($p = 0.025$ and $p = 0.002$). At 1 minute and 3 minutes after intubation, HR in group P was higher than in group C ($p = 0.026$ and $p = 0.016$).

**Adverse reactions**

Common adverse reactions in two groups included injection pain and hypotension (Table 3). Group C experienced significantly less injection pain than group P ($p = 0.001$). However, there were no significant differences in the incidence of adverse reactions, such as respiratory depression, hypotension, allergies, muscle tremors, bradycardia, postoperative nausea, and vomiting, between the two groups ($p > 0.05$).

<table>
<thead>
<tr>
<th>adverse reactions</th>
<th>Group C (N = 23)</th>
<th>Group P (N = 30)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory depression</td>
<td>1 (4.3%)</td>
<td>2 (6.7%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Injection pain</td>
<td>1 (4.3%)</td>
<td>15 (50%)*</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (4.3%)</td>
<td>6 (20%)</td>
<td>0.208</td>
</tr>
<tr>
<td>Allergy</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Muscle tremors</td>
<td>0</td>
<td>1 (3.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
All data are presented as n (%) and *p < 0.05.

Discussion

Ciprofol, an isomer of propofol with an added cyclopropyl group to its chemical structure, works by enhancing Cl- influx through GABA receptors. It activates GABAergic neurons and induces hyperpolarization of nerve cell membranes, leading to central nervous system inhibition and subsequent sedative or anesthetic effects. The purpose of this study was to determine the ED$_{50}$ and ED$_{95}$ of ciprofol and propofol for suppressing the cardiovascular response to tracheal intubation and to compare the incidence of adverse reactions between the two drugs. The experiment revealed that the ED$_{50}$ values for ciprofol and propofol in inhibiting the cardiovascular response to tracheal intubation were 0.326 mg/kg and 1.541 mg/kg, respectively. Ciprofol demonstrated more stable hemodynamics and a significantly lower incidence of injection pain during induction compared to propofol.

The findings of our study suggest that the dosage equivalent to 0.326 mg/kg of ciprofol is 1.541 mg/kg for propofol. Moreover, Ciprofol exhibits a relative potency that is approximately 4.73 times higher than propofol. This aligns with effective doses reported in earlier phase I-III studies and provides a more precise estimation. Our study reveals a slightly higher effective dose of ciprofol compared to the 0.3 mg/kg recommended by Wu, Ding, and Duan. This variation may be due to the different stimulation intensities between fiberoptic bronchoscopy and tracheal intubation, and the use of topical anesthesia in Wu's study prior to bronchoscope insertion. It is worth noting that although Ding and Duan used ciprofol for induction of general anesthesia during tracheal intubation, their study subjects focused on elderly participants. The influence of age on the pharmacokinetics and pharmacodynamics of anesthetic drugs may heighten the sensitivity of these patients, consequently necessitating lower effective doses.

Contrasting these findings, a recent study by Pei et al. on pediatric tonsillectomy using ciprofol with low-dose rocuronium bromide reported that the optimal induction dose of ciprofol was 0.6 mg/kg, significantly higher than the doses in our study and other recommendations. This discrepancy may be attributed to variations in experimental protocols, outcome measures, and the unique physiological structure of children. The findings above emphasize the need for anesthesiologists to adjust ciprofol dosage appropriately, considering relevant factors, to enhance anesthesia safety during different procedures and among diverse patient populations. Furthermore, additional literature reports suggest that ciprofol doses ranging from 0.3 to 0.5 mg/kg are effective for tracheal intubation. Our study builds on these findings, providing a more precise dosage recommendation to enhance the safety and efficacy.

Zhong's study reported that the incidence of cardiovascular adverse events related to ciprofol, including hypotension, bradycardia, and prolonged QTc interval, was comparable to that of equipotent doses of propofol. Our findings align with Zhong's study, yet we observed a more notable decrease in
heart rate within the ciprofol group, with blood pressure remaining comparatively stable. Deng et al. also found that ciprofol maintained higher values for systolic and diastolic blood pressure, and mean arterial pressure area under the curve, indicating its stable hemodynamic profile compared to propofol. Liao et al. drew similar conclusions, attributing the higher heart rate in the propofol group to injection pain and coughing.

However, our study suggests that the heart rate in the propofol group was consistently higher than in the ciprofol group at 1 and 3 minutes post-intubation ($p < 0.05$). This leads us to consider the possibility that ciprofol may exert a stronger inhibitory effect on the sympathetic nervous system compared to propofol. Intriguingly, studies by Hu et al. and Bian et al. observed an increase in heart rate in healthy subjects following ciprofol injection, but this effect emerged more than ten minutes post-injection. Pei et al. noted a significant increase in heart rate in pediatric patients post ciprofol administration, persisting until the end of induction and tracheal intubation. Given that their study was conducted in children, it remains uncertain whether this result is associated with the robust compensatory capacity of the pediatric cardiovascular system.

Injection pain is a common adverse reaction associated with propofol administration, which can amplify patient tension and anxiety, consequently affecting the stability of anesthesia induction. Our research found a significantly lower incidence of injection pain with ciprofol compared to propofol ($p = 0.001$). In the ciprofol group, only one case (4.3%) reported mild vein injection pain, while in the propofol group, 15 cases (50%) experienced this discomfort. This substantial difference highlights ciprofol's pharmacological benefit in reducing injection pain. Possible contributing factors include its unique chemical structure, emulsion formulation, high potency, and smaller injection dosages.

Nevertheless, our study is not without limitations. Participant selection was confined to young patients, excluding individuals with ASA III or IV diseases and cardiovascular conditions. Additionally, the study was a small-scale, single-center trial. Therefore, future research will focus on large-scale, multi-center trials to more comprehensively evaluate ciprofol's effectiveness and safety in a broader range of patients, including those with ASA III or IV.

**Conclusion**

In summary, our study establishes that a ciprofol dose of 0.326 mg/kg is comparable to 1.541 mg/kg of propofol. Ciprofol administration results in more stable hemodynamics and a reduced incidence of adverse events compared to propofol. These findings suggest that ciprofol could be a viable alternative to propofol in various clinical settings.

**Declarations**

**Acknowledgments**
Thanks to all the patients, doctors, and nurses who participated in this experiment.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions


Funding

This work was supported by Hainan Province Clinical Medical Center.

Data Availability Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics statement

This study project has been approved by the Ethics Committee of the Second Affiliated Hospital of Hainan Medical College. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants’ legal guardians/next of kin.

References


**Figures**

![Flowchart of study participant enrollment.](image)

**Figure 1**

Flowchart of study participant enrollment.
Figure 2

The sequential plots of the effects of ciprofotol and propofol in inhibiting cardiovascular responses to tracheal intubation were determined through an up-and-down method.

Panel A represents the propofol group, panel B represents the ciprofotol group. White circles indicate positive tracheal intubation response, while black circles indicate negative tracheal intubation response.
Figure 3

Dose-response curves of propofol and ciprofol.

Panel A shows the dose-response curve of propofol, with ED$_{50}$ and ED$_{95}$ for inhibiting cardiovascular responses to tracheal intubation being 1.541 mg/kg (95% CI 1.481-1.599 mg/kg) and 1.656 mg/kg (95% CI 1.599-1.943 mg/kg). Panel B shows the dose-response curve of ciprofol, with ED$_{50}$ and ED$_{95}$ for
inhibiting cardiovascular responses to tracheal intubation being 0.326 mg/kg (95% CI 0.304-0.337 mg/kg) and 0.349 mg/kg (95% CI 0.337-0.470 mg/kg). CI=confidence interval, ED=effective dose.

Figure 4
Comparison of blood pressure and heart rate during induction in Group C and Group P patients.
T1~T8 represent the average values of three measurements after entering the room as baseline, after intravenous administration of test drugs, after complete injection of all drugs, immediately before intubation, immediately after intubation, 1 minute after intubation, 2 minutes after intubation, and 3 minutes after intubation. * Compared to Group P, Group C showed a $p \leq 0.05$ for blood pressure or heart rate at the corresponding time point. ** Group C showed a $p \leq 0.01$ for blood pressure or heart rate at the corresponding time point when compared to Group P.